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IN SILICO IDENTIFICATION OF BIOISOSTERIC ANALOGS

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Bioisosteric replacement can be defined as the replacement of a part of a bioactive molecule with another group that is similar in size, exhibits similar physicochemical properties and maintain also the original bioactivity of the molecule. Bioisosteric transformations are used in the process of lead optimization to improve the properties of potential drug candidates, such as selectivity or transport characteristics, or to remove unwanted side effects such as toxicity and metabolic liabilities. Bioisosteric replacements are also often used in situations where the optimizations are intended to improve the synthetic accessibility of the molecule.

Identifying bioisosteric analogues of more complex groups is not trivial. This requires a considerable amount of medicinal chemistry experience. Although even if this experience is available, the identification of a bioisosterically suitable group with an optimal balance of steric, hydrophobic, electronic and hydrogen-bonding properties, all of which influence ligand-receptor interactions, usually requires an intensive procedure of trial and error.

In silico methods have been shown to provide useful help in the navigation of the functional group and scaffold spaces and the identification of proper bioisosteric analogs. These methods apply various cheminformatics techniques, such as bioactivity guided database mining, characterization of groups by a range of calculated descriptors and identification of bioisosteric functional pairs based on the similarity between their properties. An overview of these approaches will be the topic of this presentation. Various web tools developed at Novartis and successfully applied to support medicinal chemistry projects will be also presented.

Related literature :
Ertl P. et al. *J. Comp. Aided Mol. Des.*, 2012, **26:** 1207-1215.
Ertl P. *Bioorg. Med. Chem.*, 2012, **20:** 5436-5442.
Langdon S. et al. *Mol. Inf.*, 2010, **29:** 366-385.